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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/675,509

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Chandler Fulton

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EXAMINER

TON, THAIAN N

ART UNIT

PAPER NUMBER

1632

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

01/25/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

09/675,509

Applicant(s)

FULTON ET AL.

Examiner

Thaian N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 November 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10 and 33-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10, 33-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1/10/06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 11/8/06, has been entered. Claim 10 is amended; claims 33-39 are newly added. Claims 10, 33-39 are pending and under current examination.

Information Disclosure Statement

Applicants' IDS, filed 10/10/06, has been considered.

Claim Rejections - 35 USC § 112 - Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated bacterium selected from the group consisting of avirulent *C. sporogenes*, avirulent *C. beijerinckii*, and attenuated, non-pathogenic *S. typhimurium*, transfected with a vector comprising a recombinant nucleic acid sequence encoding thiaminase I from *N. gruberi* as set forth in SEQ ID NO: 3, wherein the recombinant nucleic acid sequence is operably linked to a promoter.

The specification does not reasonably provide enablement for the breadth of the claims, which encompass bacteria that comprise a recombinant nucleic acid sequence encoding thiaminase I from *N. gruberi*, as set forth in SEQ ID NO: 3, absent an expression vector or plasmid, wherein the recombinant nucleic acid is not operably linked to a promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This is a new ground of rejection, necessitated by Applicants' amendment to the claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claims are directed to a bacterium selected from the group consisting of avirulent *C. sporogenes*, avirulent *C. beijerinckii*, and attenuated, non-pathogenic *S. typhimurium*, comprising a recombinant nucleic acid sequence encoding thiaminase I from *N. gruberi* as set forth in SEQ ID NO: 3.

Breadth of the claims. The breadth of the claims encompasses the above-described bacteria comprising the recombinant nucleic acid encoding thiaminase I from *N. gruberi*, as set forth in SEQ ID NO: 3, in the absence of a vector.

Guidance of the Specification/The Existence of Working Examples. The specification teaches that thiaminase I is isolated from *N. gruberi*, a unicellular eukaryote. See p. 16, 1st ¶. The specification teaches that thiaminase I from *N. gruberi* can induce apoptosis in cells, and that various bacteria can be transfected with the nucleic acid and induce apoptosis (see page 18, lines 20-24, for example). Various bacteria can be transfected to expression thiaminase I, including the claimed bacterium, as well as *E. coli*. See page 10, lines 19-24. The specification teaches the isolation and purification of thiaminase I from *N. gruberi* (Example 3), the genomic isolation and sequence of the thiaminase I gene (pages 24-25); the expression of the thiaminase, utilizing a recombinant pET-22b(+) plasmid (p. 26, lines 8-21).

State of the Art/Predictability of the Art. The state of the art teaches that in order to express a particular protein of interest in bacterium, a vector (such as a

plasmid or bacteriophage) is required. For example, *Encyclopædia Britannica online* teaches the general concepts of genetic engineering in bacteria (“genetic engineering”. (2007). In *Encyclopædia Britannica*. Retrieved January 21, 2007, from Encyclopædia Britannica Online: <http://www.search.eb.com/eb/article-9036395>), in particular, that recombinant DNA technology involves the insertion of foreign genes into the plasmids of common laboratory bacterial strains, wherein the plasmids, although not part of the organism’s genetic information, are capable of directing protein synthesis, and the DNA is reproduced and passed on. See 2nd ¶. This is further supported by *Current Protocols in Molecular Biology*, (2002), Section 1.1-1.03 and 1.51-1.5.17 (John Wiley and Sons), who teach that vectors are used to introduce foreign DNA into *E.coli*, and that these vectors are derived from plasmids, bacteriophage lambda and related phage (see p. 1.01, 2nd ¶). In particular, they teach that plasmids are self-replicating, extrachromosomal DNA molecules, that have many different varieties in nature. In particular, they teach that vectors for the propagation, manipulation and delivery of specific fragments were constructed using these naturally occurring plasmids. In particular, they teach that plasmids have three common features, a replicator, a selectable marker, and a cloning site. The replicator contains the site of DNA replication, the selectable marker is used to maintain the presence of the plasmid in the cell, and the cloning site is where the foreign DNA is inserted. See p. 1.5.1, col. 1-2, bridging ¶. Page 1.5.11, discusses using plasmid vectors for non-*E.coli* bacteria (such as those in the instant claims). They teach that the three features of bacterial plasmid vectors are required for non-*E. coli* bacteria (see 2nd col., last ¶) and that various considerations, such as the ability to replicate and be stably maintained are important when selecting a particular vector.

The Amount of Experimentation Necessary. Thus, given the state of the art, which teaches that in order to transfect a bacteria with foreign DNA (in the instant case, with DNA that encodes thiaminase I from *N. gruberi*), a vector would be

required for expression of the DNA. The DNA must be operably linked such that it can be expressed using the vector.

Accordingly, given the state of the art, which requires a vector for the expression of foreign DNA in a bacterium, the lack of guidance or teachings in the specification to express the thiaminase I nucleic acid in the absence of a vector, it would have required undue experimentation for one of skill in the art to make and use the claimed invention.

Written Description

Claims 34-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new ground of rejection, necessitated by Applicants' amendment.

Applicants have now added claims 34-35, which are directed to a purified, enriched, or isolated nucleic acid sequence encoding thiaminase I from *N. gruberi*, wherein said nucleic acid sequence is at least 90% identical to an equal length sequence of at least 200 nucleotides in length of the *N. gruberi* thiaminase sequence as set forth in SEQ ID NO: 3. Further embodiments recite that the nucleic acid sequence comprises a sequence at least 95% identical to the sequence of SEQ ID NO: 3.

Applicants' Arguments. Applicants state that these claims are based on original claims 8 and 18-19 that were amended in response to the Final Office action, dated April 21, 2006. Applicants point out that claims 18-19 were rejected in the Office action dated 1/26/06, and that the elements of the combination of, "both 90% identical to an equal length of at least 200 nucleotides" are not named together, and hence the combination allegedly lacked written description. Applicants argue

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that the specification states that one of skill in the art would recognize that the invention is described in terms of any individual member or subgroup of the Markush group or other groups recites in the specification. Furthermore, Applicants argue that this claim has basis in the specification on page 11, lines 21-25. Thus, Applicants argue that in view of the use of Markush and other groups in the specification, as discussed on p. 40, lines 13-16, as well as each of the 6 percentages and 12 nucleotide lengths, explicit support for the combination (90% and 200 nucleotides) is found in the specification. See pages 5-6 of the Response, field 11/8/06.

Response to Arguments. These arguments are not found to be persuasive. In particular, newly added claims 34-35 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 34 recites that the nucleic acid sequence must encode thiaminase I, and is at least 90% identical to an equal length of at least 200 nucleotides in length of SEQ ID NO: 3. Thus, the Examiner provides this reasoning:

1. SEQ ID NO: 3 is 1068 nucleotides in length.
2. 200 nucleotides of the total length is approximately 18.7%
3. 90% identical to an equal length of 200 nucleotides is 180 nucleotides.

Thus, Applicants are claiming a sequence that must encode thiaminase I, and that is at least 180 nucleotides identical to an equal length sequence that is only 18.7% of the total length of SEQ ID NO: 3. Thus, given this analysis, nearly 82 percent of the sequences can be different, and yet still encode thiaminase I. The specification provides no description for such a sequence. In fact, the portion of the specification that Applicants cite as support for the percentage and sequence length of this sequence is directed to an isolated, purified or enriched nucleic acid molecule. There is no recitation that this molecule would encode a functional thiaminase I,

with enzymatic activity. Thus, the specification does not convey to one of skill in the relevant art that the inventors at possession of the claimed invention.

Furthermore, with regard to Applicants' citation regarding Markush groups, it is noted that written description requires that applicants show that they have possession of the claimed invention. MPEP §2163 states:

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

The portion of the specification that Applicants have pointed to amounts to a "laundry list" of various percentages and nucleotide lengths, but it would not lead those of skill in the art to any particular combination, and, in particular, the specific combination that Applicants' claim.

These embodiments are not specifically named together, such that one of skill would recognize that the nucleic acid sequence would encode thiaminase I, and thus, the combination of the two lacks a written description. Additionally, the specification does not provide support for a nucleotide sequence is of equal length to 200 nucleotides in length of SEQ ID NO: 3, there is no contemplation of an "equal length" in the specification. Furthermore, the claim recites that the nucleic acid sequence is at least 90% identical to "an equal length sequence of at least 200 nucleotides in length". This lacks written description because, although thiaminase I from *N. gruberi*, as encoded by SEQ ID NO: 3, has been adequately described, as set forth in the prior Office action, there is no specific description provided by the specification for any other sequences with specific percentage identity to specific nucleotides of SEQ ID NO: 3, which, when constructed and used as claimed, would

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encode thiaminase I from *N. gruberi*, and be capable of inducing apoptosis in vertebrate cells.

Accordingly, the specification fails to meet the written description requirement with regard to the claimed embodiment of nucleic acid sequences encoding thiaminase I isolated from from *Naegleria gruberi*, wherein the nucleic acid sequence is at least 90% or 95% identical to an equal length of at least 200 nucleotides in length of SEQ ID NO: 3 lacks written description.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new ground of rejection, necessitated by Applicants' amendment to the claims.

Claims 10 and 33 are unclear. In particular, the claims recite a vector comprising a recombinant nucleic acid sequence encoding thiaminase I from *N. gruberi* as set forth in SEQ ID NO: 3. The metes and bounds of these claims are unclear, as this language encompasses the vector that comprises the nucleic acid sequence to be set forth in SEQ ID NO: 3, or, alternatively, simply the nucleic acid sequence is set forth in SEQ ID NO: 3. Appropriate correction is required.

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Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thaian N. Ton

THAIAN N. TON
PATENT EXAMINER